REMARKS

Claims 8-12, 18, 21, 22, 26, 27, and 30-38 were rejected by the Examiner. In light of the following remarks and the attached declaration, Applicant respectfully requests reconsideration and allowance of all pending claims.

Rejections under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 8-12, 18, 21, 22, and 26 under 35 U.S.C. § 103(a) as being unpatentable over Tovey *et al.* (U.S. Patent No. 5,997,858) in view of Brittenden *et al.* (*Cancer* 77:1226-1243, 1996). The Examiner stated that the Tovey *et al.* patent teaches administering alpha-interferon in doses ranging from 5000 U to $20x10^6$ U, and preferably ranging from $1x10^4$ U to $1x10^6$ U. The Examiner further stated that the dosages recited in the Tovey *et al.* patent, when converted to the units used in the instant application, range from about 475,000 U/man to about 950,000 U/man. Thus, the Examiner stated that the narrowest range of dosages disclosed in the Tovey *et al.* patent encompasses the presently claimed range of dosages. Because of this, the Examiner further stated that the Tovey *et al.* patent inherently teaches the methods of present claims 9-12.

The Examiner also stated that while the Tovey *et al.* patent fails to teach a method that includes determining NK cell cytotoxicity, the Brittenden *et al.* reference teaches that alpha-interferon enhances NK cell activity, and that NK cell activity plays an important role in natural cytotoxicity of cancer cells. Thus, the Examiner alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to add steps of measuring NK cell cytotoxicity to the methods disclosed in the Tovey *et al.* patent. The Examiner also stated that the ability of alpha-interferon to increase NK cell activity is an inherent effect of alpha-interferon administration, as evidenced by the teachings of the Brittenden *et al.* reference.

In addition, the Examiner maintained the rejection of claims 27 and 30-38 under 35 U.S.C. § 103(a) as being unpatentable over Markovic *et al.* (*Int. J. Cancer* 45:788-794, 1990) in view of the Tovey *et al.* patent. The Examiner stated that the Markovic *et al.* reference teaches that alpha-interferon acts to increase NK lymphocyte cytotoxicity, and that increased NK cytotoxicity is desired in the surgical treatment of cancer. The Examiner further stated that the

Markovic *et al.* reference teaches a method for surgical removal of tumors from mice treated with alpha-interferon prior to surgery. In addition, the Examiner stated that while the Markovic *et al.* reference fails to teach either methods for treating humans or dosages that increase NK lymphocyte cytotoxicity by at least 50% or at least 75%, the Tovey *et al.* patent teaches dosages of alpha-interferon in humans that stimulate the immune system and that encompass the instantly claimed range of dosages. Thus, the Examiner alleged that the dosage range recited in the present claims appears to be an optimization of the prior art range. The Examiner further alleged that it would have been *prima facie* obvious to one of skill in the art to combine the teachings of the Markovic *et al.* reference with the teachings of the Tovey *et al.* patent to devise a method for treating humans. Moreover, the Examiner stated that the Declaration by Dr. Markovic submitted with the response to the previous Office Action was incomplete, and thus could not be used to assess Applicant's assertion concerning the criticality of the claimed dosage levels.

Applicant respectfully disagrees with these rejections. Applicant also disagrees with the dosage calculations provided by the Examiner with regard to the Tovey *et al.* patent. The dosages disclosed in Tovey *et al.* patent range from 1500 U/man to $20x10^6$ U/man for a 70 kg man. See, the Tovey *et al.* patent at column 2, lines 25-32. These values convert to a range of 806 U/m^2 (i.e., 1500 U/1.86 m^2) to 10,752,688 U/m^2 (i.e., $20x10^6$ U/1.86 m^2) if, as stated by the Examiner, the average 70 kg man has a surface area of about 1.86 m^2. This range is extremely broad. Even the "preferred" range of Tovey *et al.*, from 5376 U/m^2 (i.e., $1x10^4$ U/1.86 m^2) to 537,634 U/m^2 (i.e., $1x10^6$ U/1.86 m^2), covers a 100-fold difference in potential dosages. The instant claims, in contrast, recite dosages ranging from about 250,000 U/m^2 to about 500,000 U/m^2, a range that encompasses only a 2-fold difference in potential dosages. As indicated in the enclosed Declaration under 37 C.F.R. § 1.132 by Dr. Markovic, dosages below 250,000 U/m^2 and above 500,000 U/m^2 would not be immunostimulatory. The Tovey *et al.* patent fails to suggest that the particular range of dosages recited in the present claims is critical to achieve an immunostimulatory response. In fact, in the Declaration Dr. Markovic attests that the criticality of the presently claimed range could not have been predicted from reading the Tovey *et al.* patent.

The MPEP states that "Applicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range." MPEP § 2144.05. As

indicated in the enclosed declaration and supporting figures, dosages of alpha-interferon at 250,000 U/m^2, 325,000 U/m^2, and 500,000 U/m^2 were effective to increase NK cell cytotoxicity in the patients studied. The dosage of 250,000 U alpha-interferon/m^2 was more effective than the dosage of 500,000 U alpha-interferon/m^2, and the dosage of 325,000 U alpha-interferon/m^2 was significantly more effective at eliciting an immunostimulatory response than either the higher dosage or the lower dosage. Thus, Applicant declares that dosages of alpha-interferon lower than 250,000 U/m^2 or higher than 500,000 U/m^2 would not be immunostimulatory, and that the claimed range is critical for the clinical success of the claimed methods. Applicant further attests that the criticality of the claimed range could not have been predicted based on the teachings of the Tovey *et al.* patent. This is particularly true given that the Tovey *et al.* patent teaches using dosages both above and below the presently claimed range.

Thus, Applicant submits that the claimed methods are not obvious over the cited references. Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

Applicant respectfully submits that claims 8-12, 18, 21, 22, 26, 27, and 30-38 are in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned if such would further prosecution.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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